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Sodium bicarbonate administration for metabolic acidosis in the intensive care unit: a target trial emulation

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Abstract

Purpose: Sodium bicarbonate is commonly administered to treat metabolic acidosis in intensive care units (ICUs). There is limited evidence from randomized trials to support this practice, and observational studies show conflicting results. Our aim was to perform a target trial emulation evaluating the effect of bicarbonate therapy on mortality.

Methods: Retrospective cohort study using data from 12 Australian ICUs. Inclusion criteria were adults with pH < 7.3 and $PCO_2 \leq 45$ mmHg within the first three days. We excluded repeat admissions, toxicology, diabetic ketoacidosis, and pre-existing end-stage renal failure. The treatment intervention was sodium-bicarbonate administration, and the primary outcome was 30-day ICU mortality with ICU discharge as a competing event. We evaluated multiple subgroups, including patients with acute kidney injury, requirement for vasoactive therapy, and pH < 7.2. The primary model utilized a parametric g-computation and rolling entry matching was performed as a sensitivity analysis.

Results: We identified 6157 eligible admissions, of which 1764 (29%) received sodium bicarbonate. Bicarbonate therapy was associated with a 1.9% absolute mortality reduction for the primary analysis [risk ratio 0.86, 95% confidence interval (CI) 0.80 to 0.91], and significant benefits were seen across all subgroups evaluated. A similar point estimate of 2.1% was observed in the sensitivity analysis, with a sustained mortality reduction seen at 30 days.

Conclusion: In this target trial emulation, bicarbonate administration was associated with a small but statistically significant reduction in mortality for patients with metabolic acidosis. Large sample sizes would be required to demonstrate this effect in a randomized trial.

Keywords: Sodium bicarbonate, Metabolic acidosis, Critical care, Acute kidney injury

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Introduction

Metabolic acidosis is commonly encountered in intensive care units (ICUs) [1] and associated with high mortality rates [2, 3]. Detrimental effects of acidosis include impaired myocardial contractility, arrhythmias, systemic vasoplegia, pulmonary vasoconstriction, impaired response to catecholamines, and reduced immune function [4]. While management should focus on addressing the underlying cause [5], correcting acid–base status may attenuate the negative effects of acidemia [1] and allow time for other treatments to take effect [6].

Sodium bicarbonate is frequently used to treat metabolic acidosis in ICU, though the practice varies widely between different countries [7] and individual facilities [2]. Despite a logical rationale for its use, two small trials did not demonstrate that it directly improved hemodynamic parameters [8, 9]. Bicarbonate administration is associated with potential harms, including rebound alkalosis, hypocalcaemia, hypokalemia, hypotension, and thrombophlebitis [4]. Concerns have also been raised about worsening intracellular acidosis due to increased CO_2, which readily diffuses across cell membranes [10].

BICAR-ICU was an open-label randomized-controlled trial (RCT) of bicarbonate administration in 389 patients with pH < 7.2 [11]. It showed non-significant results overall for a composite of mortality and organ dysfunction, but reduced mortality in the subgroup with acute kidney injury (AKI). Observational studies report conflicting results, varying from potentially dramatic benefits [12–14] to no significant difference in outcome [7, 15–17] or even possible harm [18–20]. The use of observational data is particularly challenging, as bicarbonate is often preferentially administered to the most unwell patients [21, 22]. Robust analysis requires careful attention to potential biases as well as adjustment for confounding.

The conduct of future RCTs can be optimized by clarifying the anticipated treatment effect using well-conducted analyses of high-volume observational data. The aim of this project was to use a large, multi-center ICU dataset to perform a target trial emulation evaluating the effect of bicarbonate administration on mortality. Our hypothesis was that bicarbonate administration, compared to no bicarbonate, would reduce ICU mortality in patients with metabolic acidosis.

Take-home message

In a target trial emulation using data from 12 Australian intensive care units, bicarbonate administration was associated with a 1.9% absolute mortality reduction in patients with metabolic acidosis. Large sample sizes would be required to replicate these findings in a randomized trial, and the results support bicarbonate use in populations outside of those targeted for recruitment in ongoing clinical trials.

Methods

Study design

We performed a target trial emulation utilizing a multicenter, retrospective dataset obtained from 12 closed-model ICUs in Australia, accessed via the Queensland Critical Care Research Network. The participating sites include tertiary, metropolitan, and regional centers, and encompass the majority of intensive care to the state's population. Data sources included hospital electronic medical records supplemented by data from the Australia and New Zealand Intensive Care Society Adult Patient Database, Queensland Hospital Admitted Patient Data Collection and linkage to the Queensland Registry of Births, Deaths and Marriages. The dataset was available for admissions from January 1st 2015 to December 31st 2021.

Eligible patients were adults (age ≥ 18yrs) admitted to ICU with metabolic acidosis defined as pH < 7.3 and $PCO_2 \leq 45$ mmHg within the first three days of admission. Exclusion criteria were a history of dialysis-dependent renal failure, diabetic ketoacidosis, toxicology admissions, and repeat ICU admissions meeting inclusion criteria. We also excluded interhospital transfers and patients with transfer to an ICU as their discharge destination.

The study intervention was sodium-bicarbonate administration on days when the eligibility criteria were met. The primary outcome was 30-day ICU mortality with discharge from ICU as a competing event. As a secondary outcome, we evaluated time to renal replacement therapy (RRT) with death or ICU discharge as competing events. The frequency of bicarbonate use over time was evaluated as a potential confounder which was planned for inclusion in the multivariable model.

We performed the following subgroup analyses:

- pH < 7.3 in conjunction with AKI, defined as stage ≥ 2 on the Kidney Disease: Improving Global Outcomes (KDIGO) classification [23]
- pH < 7.3 with requirement for vasoactive treatment, consisting of a mean daily vasoactive-inotropic score (VIS) of ≥ 10, equivalent to 0.1mcg/kg/min noradrenaline [24]
- Severe acidosis with pH < 7.2
- Admissions not meeting additional severity criteria (i.e., 7.2 ≤ pH < 7.3, KDIGO stage ≤ 1, and VIS < 10)

As RRT is a major potential confounder, we performed an additional sensitivity analysis stratifying patients by whether they received dialysis during the admission.

Statistical analysis

The use of bicarbonate over time was evaluated using Kendall's τ and the Mann–Kendall test [25]. To aid visualization of the trend, a locally weighted scatterplot smoothing (LOWESS) curve was added. For unadjusted analyses, the Aalen–Johansen method was used to compute cause-specific cumulative incidence.

To evaluate the association between bicarbonate administration and mortality, we conducted a target trial emulation utilizing a parametric G-computation. This is a multi-step statistical method to estimate treatment effect using observational data with treatments, confounders, and outcomes which vary over time [26]. The technique uses regression analyses to model daily values of time-varying covariates, including treatments administered. Predictions from these regressions were utilized in outcome models for ICU mortality with ICU discharge as a competing event. Overall model performance was evaluated and adjusted based on predictions of observed patient events.

In the next step, a Monte Carlo simulation was utilized to estimate the mortality risk under different treatment strategies. Comparison of estimated mortality rates allowed calculation of risk differences, and bootstrapping with 10,000 resamples was used to estimate 95% CIs. Non-normally distributed variables were transformed or categorized as appropriate and natural cubic splines were utilized to model nonlinear relationships.

Variables utilized in the model were chosen a priori based on a known or strongly suspected relationship between treatment and outcome (i.e., likely confounders). These included age, gender, admission diagnostic group, Charlson Comorbidity Index (CCI), and admission year. Time-varying covariates were pH, HCO_3, PCO_2, highest lactate, RRT, mean VIS, and the maximal daily Sequential Organ Failure Score (SOFA). "Time zero" was defined as admission to ICU, and time-varying covariates were extracted daily for the first 30 days in intensive care. As the dataset records the day of bicarbonate administration but not an hourly timestamp, pH, HCO_3, and PCO_2 were taken from the daily blood gas with the lowest calculated Standard Base excess (SBE). Further details of the complete models are available in the electronic supplementary material (Tables S1–S3 and Figure S1).

To further assess for model misspecification, a sensitivity analysis was performed using rolling entry matching (REM). REM is a semi-parametric technique that controls for immortal time bias and time-varying confounding by matching patients on the same day of their admission. As propensity score matching is modeled around treatment allocation and the g-computation based on outcome, agreement between these techniques suggests that the model is not misspecified.

Patients treated with bicarbonate in the first three days of admission were matched, one to one with replacement, using the log of a propensity score calculated on the day of treatment. The propensity score was created using the same covariates as the main model with a 1-day lag for each variable. Marginal cumulative risk curves were estimated for ICU mortality (with ICU discharge as a competing event) and 30-day mortality using Cox proportional hazards models. The proportional hazards assumption was checked by evaluating the correlation between the scaled Schoenfeld residuals and time.

Statistical analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing, 2024) including the packages Gformula [26], Rollmatch [27], Survival, RiskRegression [28], cobalt [29], and ggplot2. Missing values for blood gas and lactate results were imputed by bringing previous values forward.

Results

Population characteristics

We identified 6157 eligible admissions, and a flowchart of patient selection is shown in electronic supplementary Figure S2. A total of 1764 patients (29%) were treated with bicarbonate, and further details regarding the timing and quantity of administration can be found in the electronic supplementary material (Tables S4-S5). The median cumulative bicarbonate dose was 150 mmol for the whole population, but varied between 100 and 200 mmol in the subgroups depending on their illness severity. The rate of administration by year of admission is shown in electronic supplementary Figure S3 and suggests a non-significant trend toward increasing use over time.

Characteristics of the study population are shown in Table 1, with a breakdown comparing patients who did and did not receive sodium bicarbonate therapy. Patients who received bicarbonate had higher APACHE III scores and more severe acidosis. They also had a greater requirement for vasoactive support and were more likely to receive RRT. Unadjusted ICU mortality was significantly greater in the cohort who received bicarbonate therapy, as seen in the survival curves in Fig. 1.

Primary and secondary outcomes

Results of the target trial emulation and sensitivity analysis are presented in Fig. 2, and Fig. 3 depicts cumulative mortality risk curves with and without bicarbonate therapy based on the g-formulation. Bicarbonate administration was associated with a small but statistically significant reduction in ICU mortality, with an absolute risk reduction (ARR) over the whole population of 1.9% (95% CI − 2.7% to − 1.3%). It was also associated with a

Table 1 Population characteristics

	No bicarbonate (*N* = 4393)	Bicarbonate (*N* = 1764)	Total cohort (*N* = 6157)
Female	1733 (39%)	714 (41%)	2447 (40%)
Age (years)	63 (49, 72)	63 (50, 72)	63 (49, 72)
Charlson Comorbidity Index			
< 4	2370 (54%)	905 (51%)	3275 (53%)
4–5	1068 (24%)	440 (25%)	1508 (25%)
6–7	500 (11%)	207 (12%)	707 (12%)
> 7	455 (10%)	212 (12%)	667 (11%)
Diagnostic groups			
Cardiovascular	1614 (37%)	74 (42%)	2358 (38%)
Respiratory	451 (10%)	133 (8%)	584 (10%)
Gastrointestinal	728 (17%)	235 (13%)	963 (16%)
Neurological	365 (8%)	76 (4%)	441 (7%)
Sepsis	400 (9%)	279 (16%)	679 (11%)
Trauma	400 (9%)	113 (6%)	513 (8%)
Other	435 (10%)	184 (10%)	619 (10%)
Apache III score	59 (44, 78)	67 (48, 96)	61 (45, 83)
Blood gas on enrollment			
pH	7.26 (7.23, 7.28)	7.22 (7.16, 7.26)	7.26 (7.20, 7.28)
PCO_2 (mmHg)	38 (± 7.1)	35 (± 7.5)	37 (± 7.3)
HCO_3 (mmol/L)	17 (14, 19)	14 (11, 16)	16 (13, 18)
Anion Gap (mmol/L)	16 (± 5.6)	19 (± 6.6)	17 (± 6.1)
Cumulative fluid balance[a] (ml)	610 (-39, 1779)	1405 (430, 2925)	818 (51, 2092)
Balanced crystalloid solution	903 (406, 1618)	800 (388, 1500)	889 (400, 1607)
Unbalanced crystalloid solution	425 (120, 976)	347 (93, 1000)	407 (112, 1000)
Colloid solution	0 (0, 500)	250 (0, 750)	0 (0, 500)
Severity of acidosis			
pH 7.2–7.3	3710 (85%)	1094 (62%)	4804 (78%)
pH 7.1–7.2	486 (11%)	426 (24%)	912 (15%)
pH 7.0–7.1	138 (3%)	158 (9%)	296 (5%)
pH < 7.0	59 (1%)	86 (5%)	145 (2%)
Average vasoactive treatment on day of enrollment			
Noradrenaline equivalent (mcg/kg/min)	0.02 (0, 0.10)	0.07 (0, 0.22)	0.03 (0, 0.13)
VIS[b]	2.0 (0, 8.8)	5.6 (0.7, 18.0)	3.0 (0, 11.0)
Ventilatory support day of enrollment			
Non-invasive ventilation	46 (1%)	23 (1%)	69 (1%)
Invasive ventilation	3143 (72%)	1384 (79%)	4527 (74%)
AKI[c] day of enrollment			
No AKI	2490 (57%)	650 (37%)	3140 (51%)
Stage 1	756 (17%)	279 (16%)	1035 (17%)
Stage 2	471 (11%)	263 (15%)	734 (12%)
Stage 3	676 (15%)	572 (32%)	1248 (20%)
RRT[d] day of enrollment	447 (10%)	369 (21%)	816 (13%)
ICU mortality	498 (11%)	356 (20%)	854 (14%)
30-day mortality	651 (15%)	414 (24%)	1065 (17%)
90-day mortality	735 (17%)	456 (26%)	1191 (19%)
Days alive and outside of ICU at day 30	27 (20, 28)	25 (7, 28)	26 (18, 28)
Days alive and without vasopressor support at day 30	28 (24, 29)	25 (16, 28)	27 (23, 29)

Data presented as n (%), mean (± standard deviation) and median (interquartile range). There were no missing data related to the above parameters for all included admissions

[a] Cumulative ICU fluid balance on day of meeting eligibility criteria. Balanced solutions = compound sodium lactate or plasmalyte solutions. Unbalanced

Table 1 (continued)

solutions = crystalloid solutions with strong ion difference of zero (e.g., 0.9% sodium chloride)

[b] *VIS* vasoactive-inotropic score;[c]*AKI* acute kidney injury;[d]*RRT* renal replacement therapy

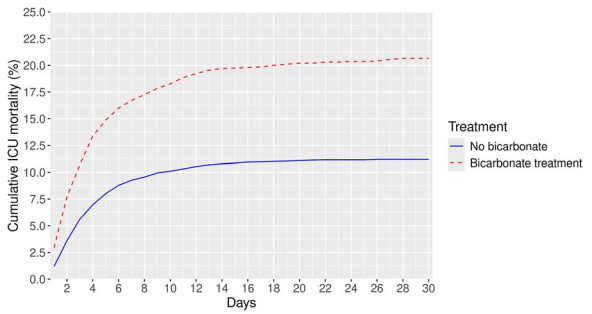


Fig. 1 Unadjusted ICU mortality[a] in patients who did or did not receive sodium bicarbonate. [a]ICU mortality with ICU discharge as a competing event

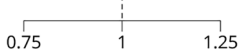
significant reduction in RRT, with an ARR of 2.5% (see Fig. 2, and electronic supplementary Figures S5-S6 for associated covariate plots and cumulative risk curves).

Subgroup analyses

Greater effects on mortality were seen in the subgroups with severe acidosis as well as acidosis associated with AKI or vasoactive requirement (Fig. 2). Further details regarding the covariate plots and risk curves for the subgroup analyses can be found in electronic supplementary Figures S7-14. Additional analyses stratified by patients who did and did not receive RRT are shown in electronic supplementary Figure S15. Bicarbonate was associated

Primary Outcome - Mortality

Model	Estimated Mortality (%) No bicarbonate	Bicarbonate	RD (95% CI)	RR (95% CI)	E-value
Primary model	13.0%	11.1%	-1.9 (-2.7 to -1.3)	0.86 (0.80 to 0.91)	1.61
n=6157					
AKI	16.5%	13.9%	-2.5 (-4.0 to -0.8)	0.85 (0.76 to 0.95)	1.63
n=1982					
Vaso-active support	26.5%	23.8%	-2.8 (-4.5 to -0.7)	0.90 (0.83 to 0.97)	1.46
n=1656					
pH < 7.2	21.3%	18.3%	-3.0 (-5.1 to -1.0)	0.86 (0.76 to 0.96)	1.60
n=1353					
pH ≥ 7.2*	6.5%	5.2%	-1.3 (-2.1 to -0.5)	0.80 (0.70 to 0.93)	1.81
n=2851					
REM: ICU	21.5%	19.4%	-2.1 (-4.9 to 0.6)	0.90 (0.78 to 1.02)	1.46
n=3370					
REM: 30-day	26.4%	23.4%	-3.0 (-5.9 to -0.1)	0.89 (0.78 to 0.99)	1.50
n=3370					



Secondary Outcome - Renal Replacement Therapy

Model	Estimated RRT use (%) No bicarbonate	Bicarbonate	RD (95% CI)	RR (95% CI)	E-value
Primary model	23.1%	20.7%	-2.5 (-3.9 to -1.1)	0.89 (0.84 to 0.95)	1.50
n=6157					

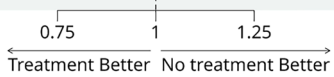


Fig. 2 Effect of bicarbonate administration on primary and secondary outcomes. *Subgroup with 7.2 ≤ pH < 7.3, no acute kidney injury or requirement for vasoactive support. *RD* absolute risk difference in estimated mortality, *RR* risk ratio, *CI* confidence interval. *AKI* acute kidney injury, *REM* rolling entry matching, *RRT* renal replacement therapy. Vasoactive support = mean daily vasoactive-inotropic score ≥ 10, equivalent to 0.1mcg/kg/min noradrenaline. E value indicates the strength of unmeasured confounding that would be required to invalidate the results. For context: in this dataset, commencing renal replacement confers an RR of 1.52 for 30-day ICU mortality

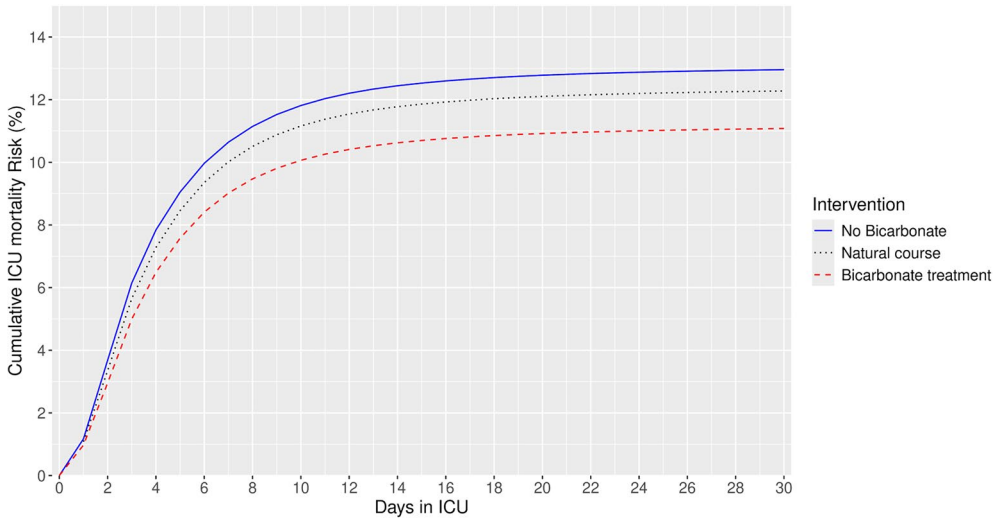


Fig. 3 Marginal ICU mortality according to use of bicarbonate therapy—g-computation. Modeled survival curves comparing treatment algorithms where no patient received bicarbonate treatment, all patients receiving treatment, or the "natural course" (i.e., the treatment which was actually administered to the patient cohort)

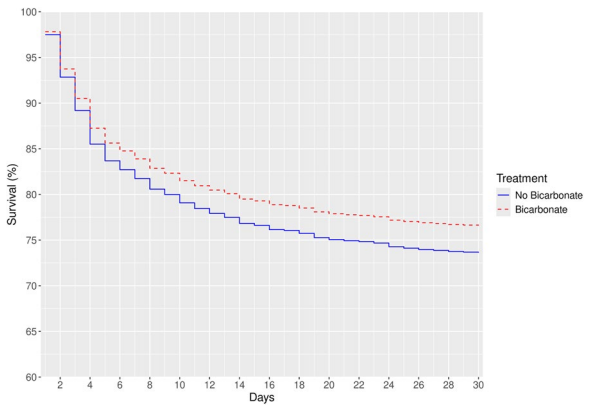


Fig. 4 Estimated 30-day survival according to use of bicarbonate therapy—rolling entry matching

with greater benefits in the cohort who were not dialysed, with an ARR of 2.1% vs 1.4% for patients who received RRT.

Sensitivity analysis

The sensitivity analysis using REM was able to match 1685 patients, giving a total population of 3370 for analysis. The analysis of ICU mortality with ICU discharge as a competing event showed a 2.1% ARR (95% CI − 4.9 to 0.6). The results were sustained and statistically significant when extended to 30-day mortality (ARR 3%, 95% CI − 5.9% to − 0.1%), with associated survival curves shown in Fig. 4. Further information regarding the REM analysis, including covariate distributional plots, can be found in electronic supplementary Figures S16–S19. Electronic supplementary Figure S20 provides additional details regarding the management of missing data.

Discussion

In a retrospective analysis of ICU patients with metabolic acidosis, sodium bicarbonate was administered in 29% of cases, with a trend to increasing administration over time. A target trial emulation of 6157 patients suggested that bicarbonate treatment was associated with a small but statistically significant mortality benefit across the whole cohort. Greater absolute benefit was seen the subgroups with AKI, requirement for vasoactive support and severe acidosis. The sensitivity analysis using REM confirmed that the mortality benefit was sustained to 30 days, and the fact that it shows similar results to the g-computation suggests that the model is well specified.

Previous observational studies evaluating the use of bicarbonate for acidosis have reported highly variable results. Some reports have described no improvement in outcomes [7, 15–17] or the suggestion of potential harm [18–20]. By contrast, a few analyses suggested an association with substantially improved outcomes, with odds ratios for mortality between 0.35 and 0.7 depending on the subgroup evaluated [13, 14]. The magnitudes of the mortality benefits in these studies seem surprisingly large considering the underlying illness severity and complex disease course of these patients. BICAR-ICU reported on

a randomized, unblinded trial of 389 patients and showed a non-significant 9% ARR in 28-day mortality [11].

Definitive evidence for bicarbonate treatment in acidosis would ideally be derived from further high-volume RCTs. To this end, there are three trials currently underway with variation in their methodology. The BICARICU-2 trial (registration number NCT04010630) will enroll 640 patients with severe acidosis ($pH \leq 7.2$) in conjunction with moderate-to-severe AKI and organ dysfunction, aiming to detect a 10% ARR in 90-day mortality [30]. The SODium BICarbonate for Metabolic Acidosis in the Intensive Care Unit (SODa-BIC) trial (NCT05697770) targets $pH < 7.3$ in conjunction with vasopressor requirement, and will recruit 500 patients to evaluate a primary outcome of major adverse kidney events [31]. The Multicentre evaluation Of Sodium bicarbonate in Acute kidney Injury in Critical Care (MOSAICC) trial (ISRCTN14027629) is enrolling patients with $pH < 7.3$ in conjunction with AKI, aiming to recruit 2250 patients to detect a 7% reduction in 90-day mortality [32].

The BICARICU-2 and MOSAICC trials target relatively high risk populations, and strongly emphasize AKI based on the significant mortality reductions seen in the subgroup analysis of BICAR-ICU [11]. In clinical practice, bicarbonate use is not exclusively restricted to patients with established renal injury, and many of the proposed benefits of correcting acidosis relate to cardiovascular function as well as renal outcomes. There may also be benefits to initiating treatment prior to meeting criteria for AKI. By contrast, the SODa-BIC trial has a more inclusive eligibility criteria, but as the primary focus is on renal outcomes, it has the lowest target for recruitment and will not be powered to demonstrate a difference in mortality between groups. At the conclusion of all these trials, it seems likely that there will be a significant proportion of patients in whom the effect of bicarbonate on mortality will remain unconfirmed.

Our analysis of high-volume observational data indicates that bicarbonate administration was associated with a small but statistically significant reduction in mortality. The disparity between these findings and BICAR-ICU may be at least partially due to differences in illness severity, as demonstrated in the baseline mortality rate which was 17% in our cohort at 30 days, compared to approximately 50% in the RCT population [11]. The two populations also differ substantially in their composition, as 60% of the patients enrolled in BICAR-ICU were treated for sepsis, while the largest diagnostic group for our population was cardiovascular pathology, with a high proportion of surgical patients. Likewise, the smaller reductions in RRT may to some extent reflect the lower overall frequency of dialysis (23% vs 53%). The RRT outcomes reported here should also be interpreted with caution due to the lack of standardized indications for commencing dialysis, which were strictly controlled in the trial protocol for BICAR-ICU.

In populations similar to ours, large numbers would be necessary to demonstrate a statistically significant benefit on mortality in a randomized trial. For example, a sample size calculation for a reduction of 2% in 30-day mortality from 18 to 16% with alpha 0.05 beta 0.8 would require 11 072 patients with complete follow-up. Significant resources would be required to conduct a trial on this scale, and it has been noted by the authors of the BICAR-ICU trial, that the risk of omitting this cheap and readily available medication may be more important than the risk of giving it in cases where the benefits have been less conclusively demonstrated [10].

Strengths and limitations

Strengths of our study include the relatively large patient cohort derived from multiple ICUs, which makes the results generalizable across a wide population. Another strength is the robust statistical methodology underpinning the target trial emulation. The parametric G-formula can be sensitive to model misspecification [33]; however, our model was shown to be very consistent in predicting the 'natural course' across all subgroups evaluated. We also performed a sensitivity analysis using modeling based on treatment allocation, which shows similar results to the primary analysis.

The study is subject to all the inherent limitations of retrospective research, including data availability and the potential for coding errors. In particular, there were no data available prior to ICU admission or following ICU discharge, including blood results, details of fluid resuscitation, or the administration of bicarbonate therapy. This meant that the primary trial emulation using g-formulation could not be extended to 30-day mortality outside ICU, as the daily values of covariates were not available. For this reason, we performed an additional sensitivity analysis with REM which provides reassurance that the reduction in mortality was sustained to 30 days. We were also unable to analyze specific details regarding the bicarbonate administration (e.g., time stamp for the hour of administration, delivery as a bolus vs infusion) as the dataset only records the total daily dose of bicarbonate therapy.

An additional limitation of target trial emulations is that the treatment effects reported can only be considered truly causal if additional assumptions are met. The positivity assumption states that all patients must have a non-zero chance of receiving treatment [34], which is likely to be true in this study as there are no known absolute contraindications to bicarbonate administration.

Additionally, the distributional plots in the supplement indicate good overlap for all the individual covariates. The consistency assumption [35] requires that exposures have a consistent effect on outcomes, which cannot be confirmed in this study as we employed a relatively simplistic treatment definition consisting of bicarbonate administration as a dichotomous variable. The dosing of bicarbonate therapy in clinical practice is further complicated by the fact that it can be administered as a finite dose or as needed to reach a certain target for correction. In our subgroup analyses, some variation in the median cumulative dose was observed between groups which likely corresponds to the quantity required to achieve correction of their acidosis.

The final major assumption of target trial emulations is exchangeability, which essentially refers to the absence of unmeasured confounders [36]. While our model uses sophisticated methods to account for both baseline and time-varying covariates, it remains possible that additional unresolved confounding may be present. Reassuringly, the E values presented in Fig. 2 suggest that a reasonably large unknown or unmeasured confounder would need to be present to invalidate the results.

Conclusion

In this target trial emulation, bicarbonate administration was associated with a small but statistically significant reduction in mortality for patients with metabolic acidosis. The benefit may be smaller than previously estimated, and large sample sizes would be required to demonstrate this effect in a randomized trial. Our analysis of high-volume observational data using robust statistical methods supports the use of bicarbonate in patients with metabolic acidosis beyond the populations targeted in ongoing randomized trials.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-025-07979-x.

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Author contributions

Sebastiaan Blank, Ruth Blank, and Mahesh Ramanan were responsible for the study conception and design, and all authors for data curation. Data analysis was performed by Sebastiaan Paul Blank. The first draft of the manuscript was written by Ruth Miriam Blank which all authors reviewed critically for important intellectual content. All authors read and approved the final manuscript.

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Data availability

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for research under Section 280 of the Public Health Act 2005 require an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

Declarations

Conflicts of interest

All authors have no conflict of interest to declare. The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and received ethics approval by the Human Research Ethics Committee at Metro South Hospital and Health Service who granted a waiver of individual consent (HREC/2022/QMS/82024). All authors have no conflict of interest to declare.

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References

1. Coppola S, Caccioppola A, Froio S, Chiumello D (2021) Sodium bicarbonate in different critically ill conditions: from physiology to clinical practice. Anesthesiology 134:774–783. https://doi.org/10.1097/ALN.0000000000003733
2. Jung B, Rimmele T, Le Goff C et al (2011) Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. Crit Care Lond Engl 15:R238. https://doi.org/10.1186/cc10487
3. Mochizuki K, Fujii T, Paul E et al (2021) Early metabolic acidosis in critically ill patients: a binational multicentre study. Crit Care Resusc 23:67–75. https://doi.org/10.51893/2021.1.OA6
4. Wardi G, Holgren S, Gupta A et al (2023) A review of bicarbonate use in common clinical scenarios. J Emerg Med 65:e71–e80. https://doi.org/10.1016/j.jemermed.2023.04.012
5. Yagi K, Fujii T (2021) Management of acute metabolic acidosis in the ICU: sodium bicarbonate and renal replacement therapy. Crit Care 25:314. https://doi.org/10.1186/s13054-021-03677-4
6. Joannes-Boyau O, Forni LG (2018) Time to treat metabolic acidosis in the ICU with sodium bicarbonate? Anaesth Crit Care Pain Med 37:493–494. https://doi.org/10.1016/j.accpm.2018.11.004
7. Fujii T, Udy AA, Nichol A et al (2021) Incidence and management of metabolic acidosis with sodium bicarbonate in the ICU: An international observational study. Crit Care Lond Engl 25:45. https://doi.org/10.1186/s13054-020-03431-2
8. Mathieu D, Neviere R, Billard V et al (1991) Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: a prospective, controlled clinical study. Crit Care Med 19:1352–1356. https://doi.org/10.1097/00003246-199111000-00008
9. Cooper DJ, Walley KR, Wiggs BR, Russell JA (1990) Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. Ann Intern Med 112:492–498. https://doi.org/10.7326/0003-4819-112-7-492
10. Jaber S, Jung B (2018) Time to treat metabolic acidosis in ICU with sodium bicarbonate? Maybe. Anaesth Crit Care Pain Med 37:499–500. https://doi.org/10.1016/j.accpm.2018.11.006
11. Jaber S, Paugam C, Futier E et al (2018) Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial. Lancet Lond Engl 392:31–40. https://doi.org/10.1016/S0140-6736(18)31080-8
12. Zhang Z, Zhu C, Mo L, Hong Y (2018) Effectiveness of sodium bicarbonate infusion on mortality in septic patients with metabolic acidosis. Intensive Care Med 44:1888–1895. https://doi.org/10.1007/s00134-018-5379-2
13. Huang S, Yang B, Peng Y et al (2022) Clinical effectiveness of sodium bicarbonate therapy on mortality for septic patients with acute moderate lactic acidosis. Front Pharmacol 13:1059285. https://doi.org/10.3389/fphar.2022.1059285
14. Huang S, Peng Y, Wang L et al (2022) Effectiveness of sodium bicarbonate infusion on mortality for elderly septic patients with acute metabolic acidosis. Front Pharmacol 13:974271. https://doi.org/10.3389/fphar.2022.974271
15. Waskowski J, Hess B, Cioccari L et al (2021) Effects of sodium bicarbonate infusion on mortality in medical-surgical ICU patients with metabolic acidosis-A single-center propensity score matched analysis. Med Intensiva S0210–5691(21):00106–00116. https://doi.org/10.1016/j.medin.2021.04.010
16. Zhang Z, Mo L, Ho KM, Hong Y (2019) Association between the use of sodium bicarbonate and mortality in acute kidney injury using marginal structural cox model. Crit Care Med 47:1402–1408. https://doi.org/10.1097/CCM.0000000000003927
17. Lo KB, Garvia V, Stempel JM et al (2020) Bicarbonate use and mortality outcome among critically ill patients with metabolic acidosis: a meta analysis. Heart Lung 49:167–174. https://doi.org/10.1016/j.hrtlng.2019.10.007
18. Wilson RF, Spencer AR, Tyburski JG et al (2013) Bicarbonate therapy in severely acidotic trauma patients increases mortality. J Trauma Acute Care Surg 74:45–50. https://doi.org/10.1097/TA.0b013e3182788fc4
19. Wang T, Yi L, Zhang H et al (2021) Risk potential for organ dysfunction associated with sodium bicarbonate therapy in critically ill patients with hemodynamic worsening. Front Med 8:665907. https://doi.org/10.3389/fmed.2021.665907
20. Kim HJ, Son YK, An WS (2013) Effect of sodium bicarbonate administration on mortality in patients with lactic acidosis: a retrospective analysis. PLoS ONE 8:e65283. https://doi.org/10.1371/journal.pone.0065283
21. Guiotto G (2024) Sodium bicarbonate in metabolic acidosis: a never-ending story? Eur J Intern Med S0953–6205(24):00511–00519. https://doi.org/10.1016/j.ejim.2024.12.016
22. Tong L, Wu S, Li D et al (2024) Hyperchloremic metabolic acidosis potentially benefiting sodium bicarbonate therapy: a multi-center cohort study. Eur J Intern Med S0953–6205(24):00411–00414. https://doi.org/10.1016/j.ejim.2024.10.001
23. Lameire NH, Levin A, Kellum JA et al (2021) Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int 100:516–526. https://doi.org/10.1016/j.kint.2021.06.028
24. Belletti A, Lerose CC, Zangrillo A, Landoni G (2021) Vasoactive-inotropic score: evolution, clinical utility, and pitfalls. J Cardiothorac Vasc Anesth 35:3067–3077. https://doi.org/10.1053/j.jvca.2020.09.117
25. Kendall MG (1938) A new measure of rank correlation. Biometrika 30:81–93
26. McGrath S, Lin V, Zhang Z et al (2020) gfoRmula: An R package for estimating the effects of sustained treatment strategies via the parametric g-formula. Patterns 1:100008. https://doi.org/10.1016/j.patter.2020.100008
27. Jones K, Chew R, Witman A, Liu Y (2019) rollmatch: an R Package for rolling entry matching. R J 11:243. https://doi.org/10.32614/RJ-2019-005
28. Gerds TA, Scheike TH, Andersen PK (2012) Absolute risk regression for competing risks: interpretation, link functions and prediction. Stat Med 31:3921–3930. https://doi.org/10.1002/sim.5459
29. Covariate Balance Tables and Plots. https://ngreifer.github.io/cobalt/. Accessed 6 May 2025
30. Jung B, Huguet H, Molinari N, Jaber S (2023) Sodium bicarbonate for the treatment of severe metabolic acidosis with moderate or severe acute kidney injury in the critically ill: protocol for a randomised clinical trial (BICARICU-2). BMJ Open 13:e073487. https://doi.org/10.1136/bmjopen-2023-073487
31. SODium BICarbonate for Metabolic Acidosis in the Intensive Care Unit (SODa-BIC): a Multicentre, Randomised, Double-blind Clinical Trial ANZIC-RC/ASN001. Registered 26th Jan 2023. Registration number NCT05697770. In: Aust. N. Z. Clin. Trials Regist. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=21026&isClinicalTrial=True. Accessed 23 Jan 2025
32. Multicentre evaluation of sodium bicarbonate in acute kidney injury in critical care (MOSAICC). ISRCTN14027629. In: ISRCTN Regist. https://www.isrctn.com/ISRCTNISRCTN14027629. Accessed 23 Jan 2025
33. McGrath S, Young JG, Hernán MA (2022) Revisiting the g-null paradox. Epidemiol Camb Mass 33:114–120. https://doi.org/10.1097/EDE.0000000000001431
34. Zhu Y, Hubbard RA, Chubak J et al (2021) Core concepts in pharmacoepidemiology: violations of the positivity assumption in the causal analysis of observational data: consequences and statistical approaches. Pharmacoepidemiol Drug Saf 30:1471–1485. https://doi.org/10.1002/pds.5338
35. Rehkopf DH, Glymour MM, Osypuk TL (2016) The consistency assumption for causal inference in social epidemiology: when a rose is not a rose. Curr Epidemiol Rep 3:63–71. https://doi.org/10.1007/s40471-016-0069-5
36. Igelström E, Craig P, Lewsey J et al (2022) Causal inference and effect estimation using observational data. J Epidemiol Commun Health 76:960–966. https://doi.org/10.1136/jech-2022-219267